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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/297,092	05/18/1999	MICHAEL PAULISTA	P564-9010	9258

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/297,092	PAULISTA ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 31 March 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *31 March 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☒ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: _____.

Claim(s) withdrawn from consideration: _____.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

JEFFREY FREDMAN
PRIMARY EXAMINER

Continuation of 5. does NOT place the application in condition for allowance because:

The declaration filed under 37 CFR 1.132 by Dr. Jens Pohl has not been considered because the declaration has not been signed under oath.

Claims 17-25, 28, 30 and 32-33 stand rejected under 35 U.S.C. 112, first paragraph, regarding enablement issues for the same reasons of record as set forth in the office action mailed on 10/01/03.

The applicant argues that the 7-cysteine region determines the 3-dimensional folding of BMPS which is decisive for receptor binding. The applicant argues that the data in the declaration (unsigned) shows that a fragment of MP52 starting with the first of the 7 conserved cysteines is active. The applicant argues that US Patent Nos. 6,426,332 and 6,281,195 show that broad claims issued on osteogenic proteins such as BMPS or GDFS as well as amino acid variants thereof have been found acceptable and enabled. The applicant argues that in the broadly granted claims of these applications, MP52 (GDF-5) as well as amino acid variants thereof are encompassed even though the examples of these patents are restricted to OP1 only and do not provide disclosure for all osteogenic proteins and/or fragments in the form of examples. The applicant argues that WO 97/04095 shows that longer fragments than the mature protein (propeptide + mature: amino acids 28-501, part of the polypeptide + mature: amino acids 48-501) are also active in the APL- assay. The applicant concluded that there is no reason to believe that MP52 fragments in combination with another protein of the TGF-b family would not have cartilage or bone-inducing activity as indicated in the present application.

However, applicant's arguments are found NOT persuasive because applicant's argument alone cannot take place of evidence lacking in the record. Each patent application is examined on its own merit and is considered enabled in view of its own disclosure. The issue is not whether the other application support their claims but whether one supports its claims "[i]t is immaterial whether similar claims have been allowed to other" In re Gialito 188USPQ 645,648 (CCPA 1976). The instant specification as filed fails to disclose that the implantation of the implant material (as claimed) leads to bone or cartilage formation in any and all animals. The specification even fails to provide a single working example that a protein encoded by SEQ ID NO:1 or its fragments (as claimed) have any bone and/or cartilage inducing potential in any and all animals. The Office has clearly provided the evidence which establishes that the signal transduction mechanism of members of TGF-beta superfamily is complex and the members are know to regulate plethora of developmental processes (Attisano et al, Science. 296:1646-1647, 20002). For example, proteins of the TGF-beta superfamily bind to two different types of signaling receptors termed as type II and type I receptors. Upon ligand binding and formation of type II and type I receptor complexes, followed by possible receptor conformational changes, type I receptors are phosphorylated and activated by type II receptor kinases. Type I receptor kinases then transmit intracellular signals by phosphorylating Smad proteins. In mammals, only five type II receptors and seven type I receptors have been identified. It is theoretically possible to form more than 30 different combinations of type II and type I receptors. However, certain type II receptors tend to interact with certain type I receptors. Thus, the combinations of type II and type I receptors appear to be limited under physiological conditions and the variety of ligands converge at the receptor level (Miyazono et al, J Cell Physiol, 187(3):265-76, 2001). The instant specification fails to disclose that MP52 modulates bone and/or cartilage formation via TGF-beta signal transduction pathway. In addition, the specification fails to disclose what are another dimmer of TGF-beta superfamily that in combination with MP52 that would leads to cartilage and/or bone formation. Thus, in order to elucidate the roles of TGF-beta and a

morphogenetic protein in clinical disorders it is very important to understand the signaling mechanisms of those proteins in vivo (see Miyazono, page 272, conclusion).

It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In instant case use of any fragment of MP52 protein (as claimed) for the treatment of any bone or cartilage defect is not considered routine in the art and without sufficient guidance to a specific therapeutic gene the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). Thus, in view of lack of specific guidance in the specification, the skilled artisan at the time of filing would be unable to use the invention as claimed, without an excessive and undue amount of experimentation. The quantity of experimentation required would include making an implant as claimed, containing fragments of MP52 protein (as claimed) in combination with any and all dimmer of TGF-beta superfamily and testing the implant for bone and/or cartilage inducing activity in vivo for the treatment of any bone defect, bone fracture, modification of jaw region (as claimed) and periodontosis.